CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
METALDEHYDE

Chemical Code # 000379, Tolerance # 50222
SB 950 # 478
10/17/86
3/17/88, 10/31/89, 7/6/90, 3/15/91, 5/17/91, 4/20/92, 9/10/93, 11/29/94, 8/25/00, 1/2/01

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, possible adverse effect.
Chronic toxicity, dog:	No data gap, possible adverse effect.
Oncogenicity, rat:	No data gap, possible adverse effect.
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome effects:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	Not required at this time.

Toxicology one-liners are attached.

All record numbers through 163302 were examined.
** indicates an acceptable study.
Bold face indicates a possible adverse effect. File name: T010102
Revised by H. Green and J. Gee, 8/25/00 and by Gee, January 2, 2001
EPA reregistration standard, dated 12/88.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

**** 50222-069; 112309** M. W. Gill and C. L. Wagner; "Chronic Dietary Toxicity/ Oncogenicity Study with Metaldehyde in Rats"; Laboratory Project ID 54-528, Bushy Run Research Center, Export, PA; January 9, 1992. Groups of 60 Sprague-Dawley CD® rats/sex were fed diets containing Metaldehyde (99% stated purity, lot # 5448) at 0 (control 1), 0 (control 2), 50, 1000, or 5000 ppm for 104 weeks. Treatment-related effects were: transient decreases in body weight gains in both sexes at 5000 ppm with group mean body weights always being > 85% of controls; increased liver weights and hepatocellular hypertrophy in both sexes at 1000 and 5000 ppm; and transient increases in serum globulin and cholesterol levels in females at 1000 and 5000 ppm (NOEL = 50 ppm). A **possible adverse effect** was indicated in females by increases in liver adenomas at 5000 ppm, hind-limb paresis at 1000 and 5000 ppm, and hind-limb paralysis at 5000 ppm (non-oncogenic NOAEL = 50 ppm). The study was unacceptable (S. Morris and J. Gee, 4/20/92) but upgraded by submission of an adequate rationale for the doses used and a copy of BRRC Project Report 51-630 (S. Morris and J. Gee, 11/29/94).

50222-066 111256 This document contains an adverse effects disclosure dated 11/11/91 for the study at 50222-069 112309. No worksheet was done (S. Morris, 4/2/92).

50222-070 111266 This document contains a revised adverse effects disclosure dated 2/24/92 for the study at 50222-069 112309. The reported incidence of adenomas plus carcinomas in the high dose females surviving to sacrifice was lowered from 14/25 in the original disclosure (50222-066 111256) to 7/25. The latter incidence was given in the final report (50222-069 112309). No worksheet was done (S. Morris, 4/2/92).

50222-078 129107 This document contains a 28-day study in which 10 Sprague-Dawley CD® rats/sex/group were fed diets containing the test material at 0, 2500, 5000, 10000, or 20000 ppm for 4 weeks. Convulsions killed 10/10 females and 4/10 males at 20000 ppm and 6/10 females at 10000 ppm. These findings provide an adequate rationale for setting the high dose in the combined chronic/oncogenicity study at 5000 ppm. Evaluation of these data changed the study status to acceptable (S. Morris and J. Gee 11/29/94).

CHRONIC TOXICITY, RAT

See combined rat.

50222-018 036085 "Long-Term Toxicity and Reproduction Studies with Metaldehyde in Rats", (National Institute of Public Health, Bilthoven, The Netherlands, 9/22/74). Two-year metaldehyde feeding study with 25 rats/sex/group at 0, 200, 1000, and 5000 ppm resulted in posterior paralysis especially at high dose where transverse spinal lesions were also found; NOEL < 200 ppm. Possible **ADVERSE EFFECT**. Complete publication, **UNACCEPTABLE**. J. Gee, 11/4/85

EPA: Data required, 12/88.

CHRONIC TOXICITY, DOG

**** 50222-021 046236** "26-Weeks-Toxicity of Metaldehyde 99%-Called "Metaldehyd"-in Beagle-Dogs After Oral Administration", (Laboratorium fur Pharmakologie und Toxikologie, Hamburg, 3/31/80). Metaldehyde, 99% pure, was administered in feed to 6 dogs/sex/group at doses of 0, 20, 60, or 90 mg/kg/day for 26 weeks. Possible **ADVERSE EFFECT. NOEL = 20 mg/kg/day** (testicular and prostate atrophy, spermatogenic arrest, and decreased erythroid parameters at 60 and 90 mg/kg/day; hepatotoxicity (hydropic swelling of hepatocytes and pericholangitis) in both sexes at 90 mg/kg/day.) Initially reviewed as unacceptable and not upgradeable as a chronic study (Davis, 12/1/86), the status was changed to unacceptable but upgradeable with information on histopathology, and diet preparation and analysis (Martz, 2/23/88). Data provided in report #071102 satisfies the requirements for histopathology and diet preparation (Chernoff, 10/20/89). Supplemental reports #088531 and #095738 contain diet preparation and dosing information, however the study was missing diet analysis (M. Silva, 3/5/91). Data in #089393 are for diet analysis. The study is now complete and **acceptable.** M. Silva, 5/13/91.

50222-058 095738 Supplemental diet data.

50222-064 089393 Supplemental diet data.

50222-037 071102 Supplemental information on histopathology and diet preparation for record no. 046236.

50222-052 088531, "Acute Studies: Addendum Product Purity" and "26-Week Dog Feeding Study: Addendum Food Mixture", (F. Camponovo, Lonza Ltd., June 7, 1990). Supplemental information on compound analysis and diet formulation for record no. 046236.

EPA: Data required, 12/88.

ONCOGENICITY, RAT

See combined rat.

ONCOGENICITY, MOUSE

Summary statement: The data gap is filled by the collective data in the two long-term studies and the 90-day study. A possible adverse effect was noted for liver toxicity. In record # 122317, liver hypertrophy was statistically significant at 300 ppm with an incidence of 34/46 in males and 15/45 in females at termination. The pathologist for record #163302 discussed the hypertrophy as part of a continuum leading to hepatocellular adenomas seen at 1000 ppm for 78 weeks. The incidence of carcinomas was not statistically significant in males or females at 1000 ppm. The earlier study, # 122317, was initially evaluated as unacceptable based, in part, on the high dose being inadequate to challenge the animals. The supplemental study, # 163302, was conducted at a single high dose of 1000 ppm. While a somewhat higher dose might have been used, this supplemental study confirmed the liver as the target organ and indicated that the liver damage, seen initially as hypertrophy in response to metaldehyde, could develop into benign adenomas. There was no significant incidence of adenomas at 300 ppm. (Gee, 8/25/00)

50222-075 122317 J. S. Chun and C. L. Wagner; "Chronic Dietary Oncogenicity Study with Metaldehyde in Mice"; Laboratory Project ID 91N0051; Bushy Run Research Center, Export, PA; 4/12/93. Groups of 60 CD-1® mice / sex were fed dietary mixtures of metaldehyde (batch # 5448, 99% stated purity) at 0 (control 1), 0 (control 2), 25, 100, or 300 ppm for 78 weeks. There were no treatment-related effects on mortality, body weight gain, food consumption, organ weights, hematology variables, or gross pathology observations. The only treatment-related effect reported was increased hepatocellular hypertrophy in both sexes at 300 ppm (NOEL = 100 ppm). There were no treatment-related oncogenic effects. No adverse effect was indicated. The study is unacceptable and not upgradeable because a maximum tolerated dose was not demonstrated (S. Morris and J. Gee, 11/29/94). Note: Purity was submitted in 3/94 (Gee, 8/24/00)

> 50222-079 129633 This document contained an adequate certificate of analysis for the test material (DPR Response, 11/29/94).

50222-105 163302, "A Chronic Dietary Oncogenicity Study with Metaldehyde in Mice", (P. Beyrouty, ClinTrials BioResearch Ltd., Senneville, Quebec, Canada, Project # 87013, 27 July 1998). [Supplemental study for record # 122317, ID 91N0051] Sixty (60) Swiss Crl:CD®-1(ICR)BR mice [same strain and supplier as in ID 91N0051] per sex per group received metaldehyde technical (100%) in the diet at 0 (control 1), 0 (control 2), and 1000 ppm (M: 135 mg/kg/day; F: 163 mg/kg/day) for 78 weeks. An additional 10 mice per sex per group (designated sentinels) received control diet and were maintained to confirm or deny a disease state in the population (if at issue). Increased food consumption (3% to 8%) was noted for males and females receiving treated diets. Absolute and relative liver weights were increased for both sexes receiving metaldehyde. Enlarged livers and increased incidence of liver masses was noted for treated males relative to controls. Non-neoplastic lesions included increased hepatocellular hypertrophy, liver necrosis, sinusoidal hystiocytosis, and

eosinophilic cell foci for treated males and females relative to controls. Neoplastic findings included increased hepatocellular adenomas for treated males (14/60 versus 4/60) and females (5/60 versus 0/60) and increased hepatocellular carcinoma for males (4/60 versus 2/60). Chronic NOEL < 1000 ppm. (liver necrosis, hypertrophy, pigment accumulation in males, others). Oncogenicity: **statistically significantly increased hepatocellular adenomas.** The incidence of carcinomas was not statistically significant. Supplemental. (H. Green and J. Gee, 8/24/00)

50222-079 129632, "Ninety-Day Dietary Dose Range Finding Study with Metaldehyde in Mice", (Michael W. Gill and Cindy L. Wagner, Union Carbide, Bushy Run Research Center, Export, PA., Project Report # 52-625, 25 September 1990). This document contained a study in which 15 CD®-1 mice per sex per group were exposed to dietary concentrations of metaldehyde technical (99% purity) at 0 (basal diet), 100, 300, 1000, 3000, or 10000 ppm (approximate mean intake levels of 19, 54, 178, 560, and 1918 mg/kg/day for males and 24, 70, 235, 742, and 2296 mg/kg/day for females) for 90 days. At 10000 ppm, five males and 1 female died within the first 8 days of treatment. There were two other deaths not related to treatment: one male at 0 ppm and one female at 3000 ppm. Treatment-related liver effects (increased liver weights, hepatocellular necrosis, hypertrophy, hyperplasia, inflammation, anisokaryosis, vacuolization, cholestasis, and biliary hyperplasia) were seen at 300, 1000, 3000, and 10000 ppm. There were no treatment-related effects that indicated mice could have not tolerated 3000 ppm for 78 weeks. No worksheet. (DPR response to data submission, S. Morris, 11/29/94; revised 8/24/00 by Green and Gee)

50222-107 "Cell proliferation and apoptosis in the liver of mice exposed to metaldehyde" (S. R. Eldridge, Pathology Associates International (PAI), Study Number 52-625-CP, April 4, 1999). Liver tissues for male and female Charles River mice from a 90-day study were examined for 1) proliferating cell nuclear antigen (PCNA), 2) apoptosis using *in situ* end labeling (TUNEL) and 3) standard histopathologic evaluation (H&E). Animals had been treated with metaldehyde in the diet at 0, 100, 300, 1000 or 3000 ppm with males being exposed in two phases. See Record 129632 in 50222-079 for the full report of the subchronic study. Centrilobular (but not periportal) cell proliferation increased with dose in both sexes. Apoptosis and binucleated cells were not affected by treatment. The retrospective study was undertaken to support a non-genotoxic mechanism for liver tumors seen in the 78-week study (Record No. 163302) but rather hepatocellular proliferation resulting from hepatotoxicity. Supplemental study. (Gee, 1/2/01)

REPRODUCTION, RAT

50222-018 036086 "Long-Term Toxicity and Reproductive Studies with Metaldehyde in Rats", (National Institute of Public Health, Bilthoven, The Netherlands, 9/22/74). Metaldehyde administered in the diet to rats at 0, 200, 1000 and 5000 ppm for 3 generations resulted in posterior paralysis with transverse spinal cord lesions, decreased fertility in males and females, decreased fertility index, lactation index, and viability index. NOEL less than 200 ppm. Possible **ADVERSE EFFECT** indicated. Complete publication, **UNACCEPTABLE** (see record no. 072992). J. Gee, 11/4/85.

50222-038 072992 "Metaldehyde Three-Generation Rat Reproduction Study", (National Institute of Public Health, Bilthoven, The Netherlands, 12/19/88). Metaldehyde, 99% pure, was administered in a semi-synthetic diet at doses of 0 (control), 200, 1000, and 5000 ppm for 24 to 28 weeks to three generations of Wistar rats. 20 females and 10 males per group were mated to produce 2 litters per generation. Hind limb paralysis in females (apparently caused by convulsion-induced trauma of the spinal cord and vertebra during gestation and delivery),

maternal death, and decreased day 21 litter size, pup weight, and pup survivability were all observed at 1000 and 5000 ppm. Possible **Adverse Health Effect**; maternal hind limb paralysis resulting in death; decreased pup weight gain and survivability. Maternal NOEL = 200 ppm (15 mg/kg) (hind limb paralysis and death); Reproductive NOEL = 200 ppm (decreased litter size, pup weight, and survivability at post natal day 21). **UNACCEPTABLE**; major variations from guideline including insufficient number of males on study; excessive maternal death at the high dose; no statistical analysis; no standardization of litter size on day 4; inadequate data for necropsies, histopathology, clinical observations, maternal weight, pup weight, gestational length, etc. Not upgradeable. Chernoff, 10/30/89.

** 50222-076 124067; "Two-Generation Reproduction Study in CD® Rats with Metaldehyde Administered in the Diet", Laboratory Project ID 91N0046; J. S. Chun and T. L. Neeper-Bradley; Bushy Run Research Center, Export, PA; 6/23/93. Dietary mixtures of metaldehyde (META®, 99% stated purity, Batch Number 5448) were given at concentrations of 0, 50, 1000, or 2000 ppm to 28 CD® rats/sex/group for two generations (F0, F1) with one litter per generation (F1, F2). At approximately 6 weeks of age, the F0 generation was continuously exposed for a 10-week pre-breeding period, a single 21-day mating period, gestation, parturition, and a 21-day lactation period. Selected F1 pups were similarly exposed beginning one week after weaning. The F2 pups were exposed through lactation until one week after weaning. Three high dose F0 females were sacrificed due to hind limb paralysis. Two of these animals had spinal cord luxations. Group mean body weights of F1 adult females at 1000 and 2000 ppm were 4 to 8% lower than controls (NOEL = 50 ppm). Group mean body weight gains for F1 and F2 pups at 2000 ppm were lower than controls during lactation. Group mean relative male and female and absolute female liver weights were increased at 2000 ppm. There were no treatment-related effects on reproductive indices. No adverse effect was indicated. The study was unacceptable (S. Morris and J. Kishiyama, 9/10/93) but upgraded by submission of an adequate certificate of purity (S. Morris and J. Gee, 11/29/94).

50222-079 129634 This document contains an adequate certificate of purity for the test material. Evaluation of these data changed the study status to acceptable (S. Morris and J. Gee, 11/29/94).

EPA: Data required, 12/88.

Note: The original finding of a possible adverse effect was based on decreased fertility and pup viability at 1000 and 5000 ppm (NOEL = 200 ppm) seen in two unacceptable studies (DPR rec. #'s 036086 and 072992). These effects appear to be secondary to the non-reproductive effects seen in these and a third

acceptable reproductive study (DPR doc. # 124067): convulsions that damaged the spinal cord and vertebra and caused hind limb paralysis in females during mating, gestation, delivery, and lactation. Hind limb paralysis is also seen in an acceptable combined rat study. For these reasons, the possible adverse effect is listed under the rat chronic toxicity data gap status and not under the rat reproduction data gap status (S. Morris and J. Gee, 11/29/94).

TERATOLOGY, RAT

** 50222-055 "Developmental Toxicity Evaluation of Metaldehyde Administered by Gavage to CD (Sprague-Dawley) Rats," (Neeper-Bradley, T. L. and Chun, J. S., Bushy Run Research Center, Union Carbide, 9/26/90, Study #: 53-517). Metaldehyde technical (99% pure, batch #: 5448) was administered by gavage to mated CD (Sprague-Dawley) rats (25/group) at 0 (corn oil), 25, 75 and 150 mg/kg/day from day 6-15 of gestation (copulation plug positive = day 0 of gestation). **No adverse effect. Maternal NOEL =** 75 mg/kg (A decrease in body weight, body weight gain, and food consumption as well as a significant increase in clinical signs and death was observed at 150 mg/kg. **Developmental NOEL** > 150 mg/kg (No effects were observed at any dose.) **Acceptable.** M. Silva, 4/1/91.

50222-062 096540 Exact duplicate of 50222-055 095218.

TERATOLOGY, RABBIT

** 50222-054 088781 "Developmental Toxicity Evaluation of Metaldehyde Administered by Gavage to New Zealand White Rabbits", (T. L. Neeper-Bradley, Bushy Run Research Center, Laboratory Project I.D. 52-655, 7/16/90). Metaldehyde, purity 99.0% was administered by gavage at concentrations of 10, 40, or 80 mg/kg/day to 16 mated female (New Zealand White) rabbits/group on days 6 through 18 of gestation. Another group of 16 mated female rabbits served as controls. **No adverse effect.** Maternal NOEL $\geq$ 80 mg/kg/day (No effects were observed at any dose). Metaldehyde may have a very sharp dose response curve, since the range-finding study showed clinical effects (rapid and labored respiration) and mortality at >100 mg/kg. ACCEPTABLE. (Kishiyama & Silva, 3/5/91).

50222-061 096539 Exact duplicate of 50222-054 088781.

GENE MUTATION

50222-018 036083 "Salmonella/Microsome Assay with Metaldehyde", (Institut fur Toxikologie, Universitit Zurich, 2/6/81). Metaldehyde; Salmonella strains TA98, TA100, TA1538, TA1537, and TA1535; 2 experiments by plate incorporation, 0-160 ug/plate (limit of solubility), plus and minus activation; no increase in revertants reported but no positive control data included and no individual plate values. **UNACCEPTABLE**. J. Gee, 11/4/85.

50222-018 036084 "Screening of 24 Pesticides by Salmonella/Microsome Assay", (Facolti di Medicina e Chirurgia, Universiti di Napoli, 1981). Metaldehyde, one of 24 pesticides screened in

Salmonella reverse mutation assay. Only summary; no data given. No mutagenicity reported. **UNACCEPTABLE**. J. Gee, 11/4/85.

50222-018 036079 Summary of 50222-018 036084.

** 50222-022 046804 "Evaluation of the Mutagenic Activity of P0071 (Metaldehyde) in an in vitro Mammalian Cell Gene Mutation Test with L5178Y Mouse Lymphoma Cells", (Notox C.V., The Netherlands 3/86). Metaldehyde (more than 99% purity) at 0, 20, 50, 100, or 200 ug/ml without S9 and 0, 20, 50, 100, or 167 ug/ml with S9 to mouse lymphoma cells (L5178Y) for 2 hours. No mutagenicity. **ACCEPTABLE**. Davis, 10/17/86.

CHROMOSOME EFFECTS

** 50222-022 046805 "Evaluation of the Ability of P0071 to Induce Chromosome Aberrations in Cultured Chinese Hamster Ovary (CHO) Cells", (Notox C. V., The Netherlands 5/86). Metaldehyde (more than 99% purity) at 0, 20, 50, or 200 ug/ml without S9 and 0, 20, 50, or 167 ug/ml with S9 to Chinese Hamster Ovary (CHO) cells for 2 hours. No mutagenicity. **ACCEPTABLE**. Davis, 10/17/86.

DNA DAMAGE

** 50222-061 096538 "Micronucleus Test in the Mouse on P0071 (Metaldehyde); OECD Guideline 474, U.S. EPA FIFRA Guideline 842; Project Number 102/64," (Jenkinson, P. C., Safepharm Laboratories, Limited, U.K., 7/17/90). Metaldehyde technical (99.3% pure; Batch #: 5448; ID #: P0071) was administered once by gavage to BKW mice at 0 (vehicle = arachis oil), 25, 50 mg/kg with a kill time at 24 hours for these doses (5 mice/sex/dose), and 100 mg/kg with kill times 24, 48 and 72 hours (5 mice/sex/time point). The incidence of micronucleated cells/1000 PCE's/animal was scored and the number of NCE/1000 PCE's was counted. There were no significant increases in incidence of micronucleated PCE's or NCE's in the treated versus the control groups. **Acceptable.** M. Silva, 5/6/91.

50222-045 087571 Exact duplicate of 50222-022 046804. Unacceptable as a DNA damage study. No new worksheet provided. Gee, 10/24/89.

NOTE: In a letter dated June 5, 1990 (in Vol. 052), the registrant states intent to generate a DNA Mutagenicity study to be performed at Hazleton Laboratories, with an anticipated completion date of March 1991.

NEUROTOXICITY

Not required at this time.

End Audit

Documents reviewed:

Document	Record #
50222-018	036079
50222-018	036083
50222-018	036084
50222-018	036085
50222-018	036086
50222-021	046236
50222-022	046804
50222-022	046805
50222-037	071102
50222-038	072992
50222-045	087571
50222-052	088531
50222-054	088781
50222-064	089393
50222-055	095218
50222-058	095738
50222-061	096538
50222-061	096539
50222-066	111256
50222-070	111266
50222-069	112309
50222-075	122317
50222-076	124067
50222-078	129107
50222-079	129632
50222-079	129633
50222-079	129634
50222-105	163302